

PTO/SB/17 (10-03)

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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$) 130.00

Complete if Known

Application Number	10/644,577
Filing Date	August 20, 2003
First Named Inventor	Connie Sanchez
Examiner Name	Not Yet Assigned
Art Unit	Not Yet Assigned
Attorney Docket No.	05432/100M919-US2

METHOD OF PAYMENT (check all that apply)☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None☐ Deposit Account:

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Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) (\$) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Total Claims	Extra Claims	Fee from below	Fee Paid
	18	-21** =		0.00
Independent Claims	1	-3** =		0.00
Multiple Dependent				

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for ex parte reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	130.00
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$) 130.00

SUBMITTED BY

(Complete if applicable)

Name (Print/Type) Jay P. Lessler

Registration No. (Attorney/Agent) 41,151

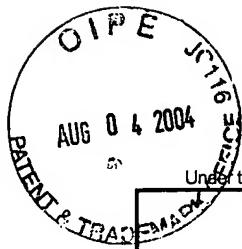
Telephone (212) 527-7765

Signature

Date August 4, 2004

Express Mail Label No.

Dated: _____



PTO/SB/21 (02-04)
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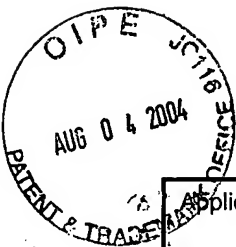
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TRANSMITTAL FORM (to be used for all correspondence after initial filing)		Application Number	10/644,577
		Filing Date	August 20, 2003
		First Named Inventor	Connie Sanchez
		Art Unit	Not Yet Assigned
		Examiner Name	Not Yet Assigned
Total Number of Pages in This Submission	1	Attorney Docket Number	05432/100M919-US2

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input checked="" type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance communication to Technology Center (TC) <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Petition to Make Special Under 37 C.F.R. §1.102 (6 pages) and Exhibits 1-5; Second Preliminary Amendment
<div>Remarks</div>		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT	
Firm or Individual name	DARBY & DARBY P.C. Jay P. Lessler - 41,151
Signature	
Date	August 4, 2004

Express Mail Label No.	Dated: _____
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Application No. (if known): 10/644,577

Attorney Docket No.: 05432/100M919-US2

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Transmittal Form (1 page);
Fee Transmittal for FY 2004 (1 page);
Petition to Make Special Under 37 C.F.R. §1.102 (6 pages and Exhibits 1-5)
Information Disclosure Statement (. pages)
Form PTO/SB/08 (1 page)
Second Preliminary Amendment (5 pages)
Check No. 6698 for \$130.00



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Docket No: 05432/100M919-US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Connie Sanchez *et al.*

Serial No.: 10/644,577

Examiner: Not Yet Assigned

Confirmation No.: 5196

Filed: August 20, 2003

Group Art Unit: Not Yet Assigned

Title: **THE USE OF ENANTIOMERIC PURE CITALOPRAM**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION TO MAKE SPECIAL UNDER 37 C.F.R. §1.102

Sir:

This is a petition pursuant to 37 C.F.R. §1.102(d) and M.P.E.P. §708.02(VIII) to advance the above-identified patent application out of turn for examination. This petition is accompanied by a check for \$130.00 to cover the fee set forth in 37 C.F.R. §1.17(h).

I. **Claims Directed to a Single Invention**

It is believed that the claims pending in this application after entry of the January 5, 2004 Preliminary Amendment and the accompanying Second Preliminary

Amendment are directed to a single invention. The present application includes one independent claim (claim 20). Claims 21-37 depend from claim 20.

Claim 20 is directed to a method of treating premenstrual syndrome in a patient in need thereof by administering to the patient a pharmaceutically effective amount of escitalopram or a pharmaceutically acceptable salt thereof as the sole active ingredient.

If the Examiner determines that all pending claims are not directed to a single invention, applicants will make an election without traverse as a prerequisite to the grant of special status.

II. Pre-Examination Search

A pre-examination search was made in International Class A 61K 31/343 by the Swedish Patent Office, as the International Searching Authority for the International counterpart (PCT Application No. PCT/DK02/00281) to this application during the International phase. The International Searching Authority conducted a search of all 19 claims in the International counterpart to the present application (International Publication No. WO 02/087566, Exhibit 1). Claim 5 of International Publication No. WO 02/087566 is directed to the use of a composition containing escitalopram (with less than 3% w/w of R-citalopram) for the treatment of patients with, *inter alia*, premenstrual syndrome.

The International Search Report and the two documents cited therein are attached as Exhibits 2-4, respectively. Additionally, the above-described international search was supplemented by the following search of U.S. patents and published U.S. patent applications:

Date of Search	July 29, 2004
Database	U.S. Patent and Trademark Office Website
Search Queries	1976-present spec/(escitalopram or s-citalopram) and spec/(pre-menstrual or premenstrual or menstrual or pms)
	1976-present aclm/(escitalopram or s-citalopram) and aclm/(pre-menstrual or premenstrual or menstrual or pms)

The above search uncovered one additional reference, namely, U.S. Patent Publication No. 2002/0103249 (Exhibit 5). Below is a discussion of the references cited in the International Search Report and the supplemental search, demonstrating how the claimed invention is patentable over each of the references.

III. Discussion of References

A. EP 347066 A1 ("EP '066") (Exhibit 3)

The U.S. counterpart to EP 347066 A1 is U.S. Patent No. Re. 34,712, which is a reissue of U.S. Patent No. 4,593,590.

EP '066 discloses the (+)-enantiomer of citalopram, and its use as an anti-depressant. See abstract.

EP '066 is completely silent with respect to the use of the (S)-(+)-isomer of citalopram (i.e., escitalopram), or a salt thereof, to treat patients with premenstrual syndrome.

Therefore, EP '066 does not disclose or suggest the method recited in the pending claims. Accordingly, claims 20-37 are patentable over EP '066.

B. WO 01/03694 (“WO ‘694”) (Exhibit 4)

WO ‘694 is directed to the use of escitalopram, and its salts, in the treatment of neurotic disorders, such as generalized anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, and panic attacks. See abstract.

WO ‘694 does not disclose or suggest the use of escitalopram to treat patients suffering from premenstrual syndrome.

Claims 20-37 are therefore patentable over WO ‘694.

C. US 2002/0103249 (“US ‘249”) (Exhibit 5)

US ‘249 is directed to the use of irindalone in combination with a selective serotonin reuptake inhibitor (SRI) or any other compound, which causes an elevation in the level of extracellular serotonin, for the treatment of depression and other affective disorders. See page 1, ¶ 1. US ‘249 states:

[T]he present invention relates to the use ... of irindalone ... for the treatment of depression, anxiety disorders and other affective disorders, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder and drug abuse, in particular depression with a serotonin reuptake inhibitor or any other compound, which causes an elevation in the level of extracellular serotonin.

See pages 1-2, ¶ 17. US ‘249 further states:

SRIs, which are particularly preferred according to the present invention, include citalopram, escitalopram, fluoxetine, sertraline, paroxetine, fluvoxamine, venlafaxine, dapoxetine, nefazodone, imipramin, femoxetine and clomipramine.

See page 3, ¶ 46. According to US '249, it was surprisingly found that irindalone may be used to augment and provide faster onset of the therapeutic effect of SRIs. See page 1, ¶ 11.

US '249 does not disclose the use of escitalopram as the sole active ingredient to treat patients suffering from premenstrual syndrome.

US '249 is a reference to the present application under 35 U.S.C. §102(e). Because US '249 and the present application were, at the time the invention claimed in the present application was made, owned by H. Lundbeck A/S or subject to an obligation of assignment to H. Lundbeck A/S, US '249 is not prior art for purposes of obviousness to the present application (35 U.S.C. §103(c)). The present application is assigned to H. Lundbeck A/S at reel 014708, frame 0097. US '249 is assigned to H. Lundbeck A/S at reel 011536, frame 0300.

Claims 20-37 are therefore patentable over US '249.

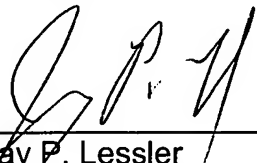
III. Conclusion

In view of the foregoing, the PTO is requested to make this application special and to accelerate examination pursuant to 37 C.F.R. § 1.102(d) and M.P.E.P. §708.02(VIII).

Favorable action is earnestly solicited.

Dated: August 4, 2004

Respectfully submitted,



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A61P 25/00, 25/22, 25/24

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(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/087566 A1

(54) Title: THE USE OF ENANTIOMERIC PURE ESCITALOPRAM

(57) Abstract: The present invention relates to the use of enantiomeric pure escitalopram and/or of low dose medicaments thereof for the improved treatment of depression, in particular major depression disorder, neurotic disorders, acute stress disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, pre-menstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse. The medicaments may also be used in the treatment of major depression disorder in "treatment resistant" patients.

The use of enantiomeric pure escitalopram

The present invention relates to the use of enantiomeric pure escitalopram (INN-name) which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, or a pharmaceutically acceptable salt thereof for the preparation of medicaments, in particular medicaments for the treatment of major depression disorder.

10 Background of the Invention

Selective serotonin reuptake inhibitors (hereinafter called SSRIs) such as citalopram have become first-choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well-tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

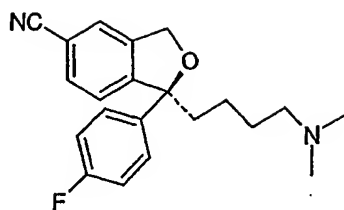
However, clinical studies on depression and anxiety disorders indicate that non-response or resistance to SSRIs, i.e. where at least a 40-60% reduction in symptoms has not been achieved during the first 6 weeks of treatment, is substantial, namely up to 30%.

Moreover, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Even in responders to SSRIs, several weeks of treatment are necessary to achieve a relief in symptoms.

In addition, sexual dysfunction is a side-effect common to all SSRIs.

Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

Escitalopram is the S-enantiomer of the well-known antidepressant drug citalopram and has the following structure:



Formula I

Escitalopram and a method for its preparation are disclosed in US Patent No 4,943,590. The stereo selectivity of citalopram, i.e. the 5-HT-reuptake inhibition in the S-enantiomer, and accordingly, its potential antidepressant effect of said enantiomer is also disclosed. It appears that substantially all the 5-HT-reuptake inhibiting effect and accordingly the antidepressant effect is in the S-enantiomer. In view of the stereo-selectivity, escitalopram is expected to be two times as potent as the racemate in the treatment depression.

WO 103694 A1 relates to the use of escitalopram in the treatment of neurotic disorders, including anxiety states and panic attacks.

It has now, surprisingly, been found that the presence of R-citalopram has a negative impact on the effect of escitalopram and escitalopram has been found in pharmacological and clinical studies to be substantially more than two times as potent as the racemate. Furthermore, escitalopram has been found to show a faster onset of action in animal models and clinical studies than the racemate and other SSRIs and to give a more full response in various animal models. Finally, clinical studies have indicated that escitalopram may be an effective medicament in the treatment of depression in patients that do not respond to conventional SSRIs.

The mechanism behind the surprising negative impact of the R-enantiomer on the effect of the S-enantiomer is not known. One possible explanation could be that the R-enantiomer may have a negative influence on the transport of the S-enantiomer over the blood brain barrier. Alternatively, R-citalopram may convey local feed-back inhibition of 5-HT release or the R-enantiomer may modulate the effect of the S-enantiomer.

Description of the invention

Accordingly, the present invention thus relates to the use of escitalopram in low doses and/or comprising less than 3 % w/w of R-citalopram for the preparation of a
5 pharmaceutical composition.

In a further aspect, the invention relates to a pharmaceutical composition characterised in that it comprises escitalopram with less than 3 % w/w of R-citalopram as an active
10 ingredient.

In yet another aspect, the invention relates to the use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of less than 10 mg of escitalopram.

15 As mentioned above, the present invention is based on the finding that R-citalopram has a negative impact on the effect on escitalopram. This may be shown in functional in-vivo pharmacological models and studies of 5-HT-reuptake effect and or in behaviour models, for example depression models.

20 Escitalopram has also been found to give a significant improvement compared to the double amount of citalopram-racemate and/or to give a more full response. So, it has been found in fixed dose studies that escitalopram in a dose of 10 mg has at least same effect as citalopram in a dose of 40 mg as determined by the MADRS rating scale and Clinical Global Impression (severity as well as improvement).

25 Escitalopram has also been found in animal models to give a faster response than citalopram-racemate. This has i.a. been found in the Chronic Mild Stress model (Willner P., Psychopharmacology 1997, 134, 319-329). This effect has been confirmed in an 8-week, double-blind, randomised, placebo-controlled, flexible-dose study that compared
30 escitalopram and citalopram to placebo in primary care patients with major depression disorder. The patients received 10 mg escitalopram (155 patients), 20 mg citalopram (160 patients) and placebo (154 patients). Escitalopram showed effects after one week whereas citalopram did not show significant effect.

All these effects are very surprising in view of the prior art suggesting that the R-enantiomer does not influence the effect of the S-enantiomer and, accordingly that escitalopram should only be twice as potent as the racemate.

- 5 As a further advantage, the fact that escitalopram is effective in lower doses suggests that effective treatment with less side effects may be obtained, in particular, a reduced amount of serotonin reuptake inhibitor may reduce the risk of SSRI-induced sexual dysfunction and sleep disturbances.

10 Detailed description of the invention

The escitalopram is preferably used as an oxalate salt, preferably a crystalline oxalate salt.

- 15 Furthermore, in the escitalopram used, R-citalopram is preferably not present in an amount exceeding 2% w/w, most preferably 1% w/w. The percentage of R-citalopram is throughout the description given as w/w % compared to the amount of escitalopram present.

- The pharmaceutical composition of the invention is preferably for the treatment of depression, in particular major depression disorder, neurotic disorders, acute stress disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, premenstrual
20 syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.

- Throughout this specification and claims the term "neurotic disorders" is used to designate a
25 group of mental disorders, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

- The terms "generalised anxiety disorder", "social anxiety disorder", "post traumatic stress
30 disorder" and "obsessive compulsive disorder" are as defined in DSM IV.

The phrase "panic attacks" contemplates treatment of any disease, which is associated with panic attacks including panic disorder, specific phobias, social phobia and agoraphobia in which panic attacks occur. These disorders are further defined in the DSM IV.

- 5 The phrase "treatment of panic disorder" means a reduction in the number or prevention of attacks and/or relief of the severity of the attacks. Similarly, the treatment of generalised anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder include the treatment or prevention of these diseases, or the relief of the symptoms thereof.

10

Based on the pharmacological and clinical studies, preferred indications are major depression disorder and obsessive compulsive disorder.

Other preferred uses are treatment of neurotic disorders.

15

- In particular, the composition may be useful for treatment of patients who have failed to respond to initial treatment with a conventional SSRI, in particular patients with major depression disorder who have failed to respond to initial treatment with a conventional SSRI. Such treatment resistant patients may in particular be defined as patients who do not
- 20 achieve an alleviation in symptoms of 40-60% by treatment with citalopram or other marketed SSRIs. Further definitions are given in Kornstein SC and Schneider RK, Clinical features of treatment-resistant depression *J Clin Psychiatr* 2001, 62, Suppl 16, 18-25; Sackeim HA, The definition and meaning of treatment-resistant depression, *J. Clin Psychiatr* 2001, 62 Suppl 16, 10-17; and Nierenber AA and DeCecco LM, Definitions of
- 25 antidepressant treatment response, remission, non-response, partial response, and other relevant outcomes: A focus on treatment-resistant depression *J Clin Psychiatr* 2001, 62 Suppl 16, 5-9.

- The pharmaceutical composition according to the invention may comprise escitalopram in a
- 30 unit dose preparation containing 2.5 to 20 mg escitalopram.

In view of the potent effect of the escitalopram used according to the invention, it may be effective in low doses, i.e. daily doses lower than 10 mg escitalopram, for example 7.5 mg

or lower, such as 7.5 or 5 mg pr day.

The pharmaceutical composition according to the invention is preferably an oral formulation, preferably a tablet.

5

Thus, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives
10 usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution
15 to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Clinical Study

20

A total of 471 patients were randomised into the study. The *all-patient-treated set* comprised 469 patients and the *full-analysis set* comprised 468 patients. In the *full-analysis set* there were 155 patients in the escitalopram group, 159 patients in the citalopram group, and 154 patients in the placebo group.

25

There was an approximately 3 to 1 ratio of women to men in each treatment group, and almost all patients were Caucasian. The mean age was 43 years (SD 11). At baseline, the mean MADRS total score was approximately 29 for the treatment group, which signifies moderate to severely ill patients.

30

The efficacy analysis of the adjusted mean change in MADRS total score showed a significantly superior therapeutic effect for escitalopram *versus* placebo from Week 1 ($p=0.023$) to Week 4 ($p=0.002$) (observed cases). At Week 4, the adjusted mean change in

MADRS total score (last observation carried forward) for escitalopram *versus* placebo was 2.7 points ($p=0.002$) compared to a statistically insignificant change of 1.5 points for citalopram *versus* placebo.

- 5 Escitalopram was significantly superior to placebo both on the CGI improvement and severity subscale from Week 1 ($p<0.05$)(observed cases) onwards, while citalopram was not statistically different from placebo during the 4-week period. At Week 4 (last observation carried forward), escitalopram was statistically significantly superior to placebo while there was no statistically significant difference between citalopram *versus* placebo.

CLAIMS

1. Use of escitalopram comprising less than 3% w/w of R-citalopram for the preparation of a pharmaceutical composition.
- 5 2. The use according to claim 1, characterised in that escitalopram is used as an oxalate salt, preferably a crystalline oxalate salt.
3. The use according to claim 1 or 2, characterised in that escitalopram comprising not
10 more than 2% w/w R-citalopram is used.
4. The use according to claim 3, characterised in that escitalopram comprising not more than 1% w/w.
- 15 5. The use according to any of Claims 1 – 4, characterised in that the pharmaceutical composition is for treatment of depression, in particular major depression disorder, neurotic disorders, acute stress disorder, eating disorders such as bulimia, anorexia and obesity, phobias, dysthymia, pre-menstrual syndrome, cognitive disorders, impulse control disorders, attention deficit hyperactivity disorder or drug abuse.
- 20 6. The use according to Claim 5, characterised in that the pharmaceutical composition is for treatment of major depression disorder.
7. The use according to Claim 5, characterised in that the medicament is for treatment
25 of a neurotic disorder.
8. The use according to any of Claims 5 to 7, characterised in that the pharmaceutical composition is for treatment of patients who have failed to respond to initial treatment with a conventional SSRI.
- 30 9. The use according to Claims 8, characterised in that the pharmaceutical composition is for treatment of patients with major depression disorder who have failed to

respond to initial treatment with a conventional SSRI.

10. Pharmaceutical composition, characterised in that it comprises escitalopram with less than 3% w/w of R-citalopram as an active ingredient.
- 5 11. Pharmaceutical composition of claim 10, characterised in that it comprises escitalopram with not more than 2% w/w of R-citalopram as an active ingredient.
- 10 12. Pharmaceutical composition according to claim 11, characterised in that it comprises escitalopram with not more than 1% w/w.
13. Pharmaceutical composition according to any of claims 10 to 12, characterised in that it is a unit dose preparation containing 2.5 to 20 mg escitalopram.
- 15 14. Pharmaceutical composition according to claim 13, characterised in that it is a unit dose preparation containing not more than 10 mg escitalopram.
15. Pharmaceutical composition according to claim 14, characterised in that it is a unit dose preparation containing not more than 7.5 mg escitalopram, preferably 5.0 mg.
- 20 16. Pharmaceutical composition according to any of claims 10 to 15, characterised in that it is a oral formulation, preferably a tablet.
17. Use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of less than 10 mg of escitalopram.
- 25 18. Use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of 7.5 mg or less of escitalopram.
- 30 19. Use of escitalopram for the treatment of major depression disorder characterised in that it is used in a daily dose of 5.0 mg of escitalopram.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 02/00281

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/343, A61P 25/00, A61P 25/22, A61P 25/24
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0347066 A1 (H. LUNDBECK A/S), 20 December 1989 (20.12.89) --	1-19
X	WO 0103694 A1 (H. LUNDBECK A/S), 18 January 2001 (18.01.01) -----	1-19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 July 2002

Date of mailing of the international search report

22-07-2002

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-19
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00281

Claims 17-19 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

06/07/02

International application No.

PCT/DK 02/00281

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
EP	0347066	A1	20/12/89	SE 0347066 T3	
				AT 119896 T	15/04/95
				AU 623144 B	07/05/92
				AU 3629589 A	04/01/90
				CA 1339568 A	02/12/97
				CY 2081 A	16/10/98
				DE 68921672 D,T	27/07/95
				DK 11593 A	01/02/93
				DK 170280 B	24/07/95
				DK 259989 A	15/12/89
				ES 2068891 T	01/05/95
				FI 91527 B,C	31/03/94
				FI 98627 B,C	15/04/97
				FI 892823 A	15/12/89
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				ZA 8904476 A	25/04/90
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				NO 20020062 A	07/01/02
				TR 200200014 T	00/00/00

(19)



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European Patent Office
Office européen des brevets

(11) Publication number:

**0 347 066
A1**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 89305532.7

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(51) Int. Cl.⁴: **C07D 307/87 , A61K 31/34 ,
//C07B57/00,C07C121/80,
C07C143/68**

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(54) New enantiomers and their isolation.

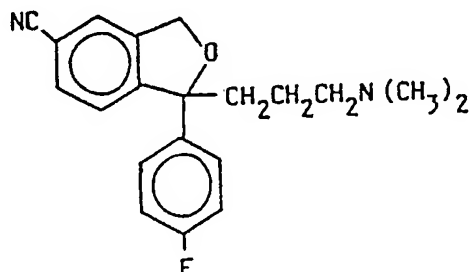
(57) The novel (+)-enantiomer of 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as well as acid addition salts thereof are described as valuable antidepressants, geriatrics or in the treatment of obesity and alcoholism.

Novel intermediates and a method for the preparation of the (+)-enantiomer as well as the racemic mixture are described.

EP 0 347 066 A1

NEW ENANTIOMERS AND THEIR ISOLATION

The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram) of the following formula I:



and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

This invention also includes pharmaceutically acceptable salts of the enantiomers of compound I formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, ethyl acetate or dichloromethane, with the desired salt separating directly. Exemplary of such organic salt are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halotheophyllines, for example 8-bromotheophylline.

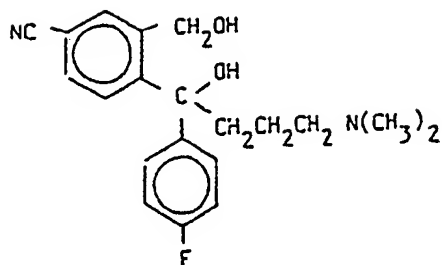
Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

Furthermore it was found that non-hygroscopic acid addition salts might be obtained by conventional freeze drying techniques from water solutions of appropriate salts of the above mentioned kinds.

The invention is also concerned with a method to resolve the racemate of I into the individual isomers.

Citalopram, which has been disclosed in eg. US Patent No. 4,136,193, has proven to be an efficient antidepressant compound in man (Ref.: A. Graven et al., Acta psychiat. Scand., No. 75, p. 478-486 (1987)). All work in the development of this compound has been made with the racemate. Citalopram has been shown pharmacologically to be a very selective inhibitor of 5-HT reuptake. Previous attempts to crystallize diastereomeric salts of citalopram enantiomers have failed.

Surprisingly, it has now proven possible to resolve the intermediate 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, II, into its enantiomers and finally in a stereoselective way to convert these enantiomers to the corresponding citalopram enantiomers. Likewise, monoesters of II formed by optically active carboxylic acids could be separated into the corresponding diastereomers and subsequently converted directly into citalopram enantiomers in a stereoselective ring-closure reaction. The intermediate diol, II, has been disclosed in eg. US Patent No. 4,650,884 as a racemic mixture.



II

The enantiomers of the intermediate of formula II as well as monoesters fall likewise within the scope of the present invention.

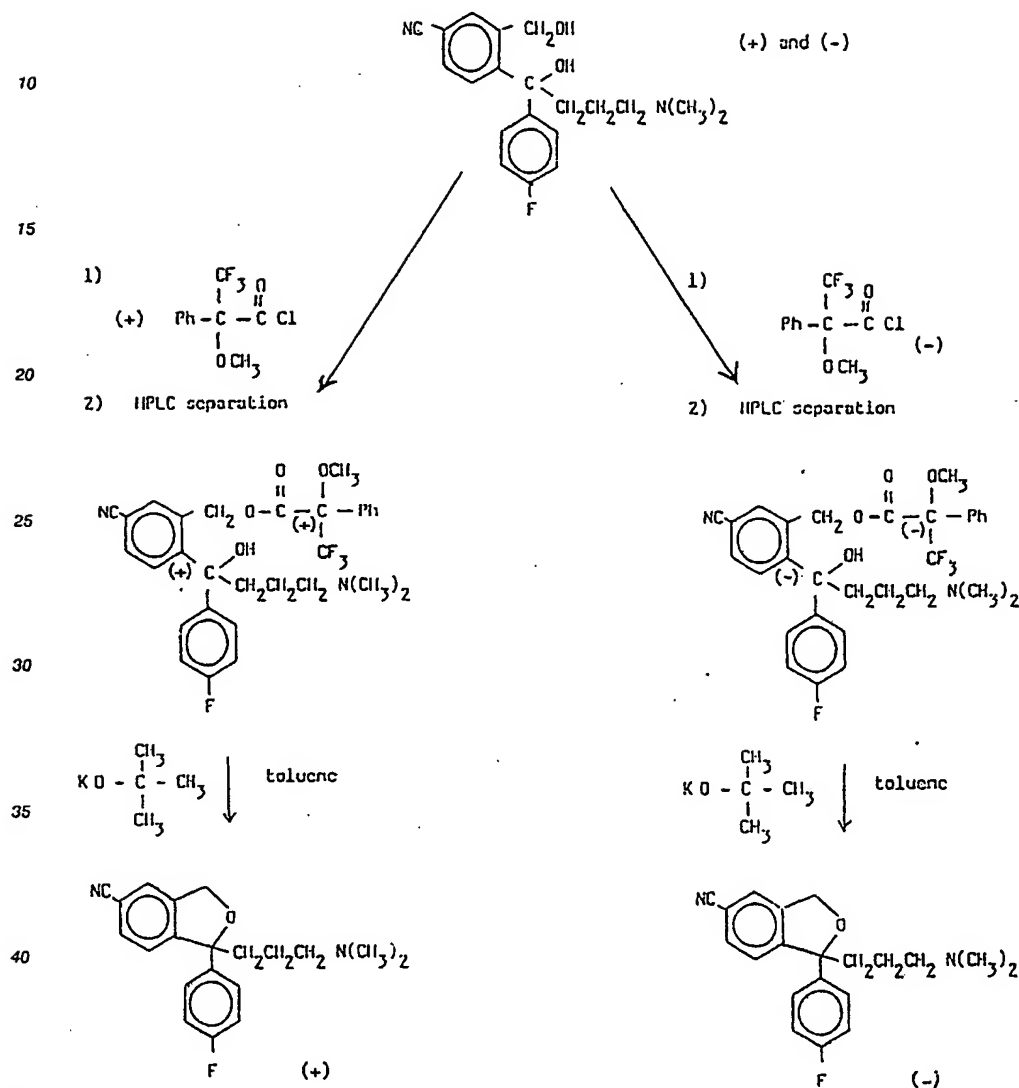
Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

The present invention also includes a new method of synthesizing I from the diol compound II by esterification of the primary alcohol group into a labile ester, which in the presence of a base undergoes spontaneous ringclosure to citalopram or, if enantiomerically pure II is esterified, the corresponding citalopram enantiomer is produced with fully conservation of stereoconfiguration.

According to the invention, II is reacted with:

a) an enantiomerically pure acid derivative as an acid chloride, anhydride or labile ester as eg. exemplified in reaction scheme I by (+)- or (-)- α -methoxy- α -trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as eg. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralize liberated HCl. The diastereoisomers are subsequently separated by HPLC or fractional crystallization. The thus purified diastereoisomers are finally separately treated with strong base (eg. alkoxide) in an inert organic solvent as eg. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at relatively low temperatures (-20°C to room temperature).

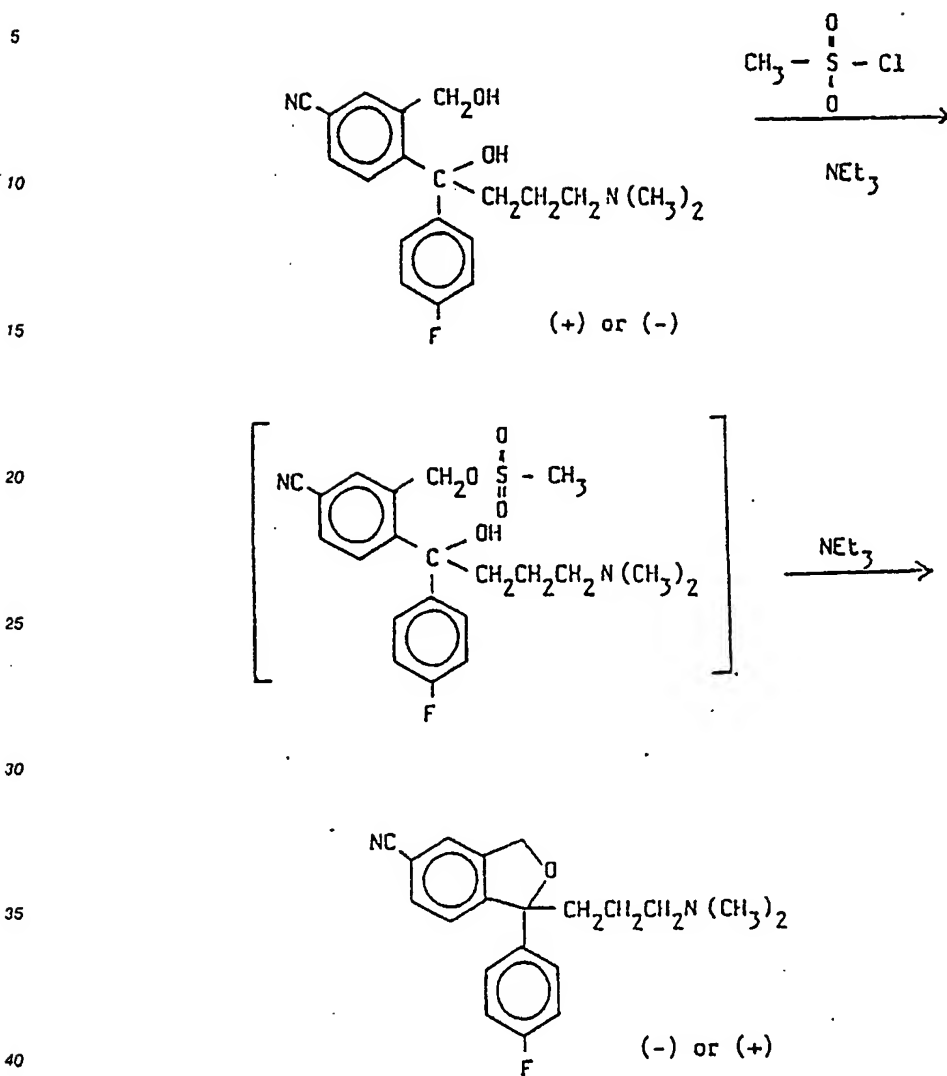
REACTION SCHEME I



b) the enantiomers of an optically active acid successively affording the pure diastereomeric salts. Optically antipodes of tartaric acid, di-benzoyltartaric acid, di-(p-toloyl)tartaric acid, bisnaphthylphosphoric acid, 10-camphorsulphonic acid and the like are conveniently used.

c) Stereoselective ringclosure of the pure enantiomers of II prepared as in b) is performed via a labile ester as eg. methansulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethansulfonyl with simultaneous addition of a base (triethylamine, dimethylaniline or pyridin) in an inert organic solvent at 0°C. The ringclosure reaction is exemplified in reaction scheme II:

REACTION SCHEME II

EXAMPLE 1Resolution by method a)

To 11 g of (+)-1-methoxy- α -trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)- α -methoxy- α -trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl-3-(hydroxymethyl)-benzonitrile, II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried (MgSO_4) and the solvent evaporated below 30°C in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated

HPLC purification (eluted with ethyl acetate / tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5-10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0°C. The toluene solution was washed with water, dried (MgSO₄) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D = +11.81^\circ$ (c = 1, CH₃OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ¹H NMR spectroscopy (CDCl₃ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (-)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D = -12.34^\circ$ (c = 1, CH₃OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.9%.

EXAMPLE 2

Resolution by methods b) and c)

To a solution of 85 gr of 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile, hydrobromide in 500 ml of water were added 200 ml of ice cooled 2 M NaOH solution and 500 ml of ether. The mixture was stirred for 1/2 hour, the ether phase separated, dried (MgSO₄) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propanol at 40°C, and 40 gr of (+)-di-p-toloyltartaric acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipitated salt was filtered off and dried yielding 29.2 gr (55.1%) of (-)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, hemi (+)-di-p-toloyltartaric acid salt. MP: 134-135°C, $[\alpha]_D = +10.0^\circ$ (c = 1, CH₃OH). The filtrate is used below.

To an ice cooled solution of 14 gr of the (-)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for 1/2 hour, washed with brine, dried (MgSO₄) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = +12.33^\circ$ (c = 1, CH₃OH).

The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D = +12.31^\circ$ (c = 1, CH₃OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently cooled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt, MP: 264-266°C, $[\alpha]_D = +13.88^\circ$ (c = 1, dimethylformamide).

A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the following manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The waterphase was freeze-dried in vacuo (< 0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the (+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, hemi (-)-di-(p-toloyl) tartaric acid salt ($[\alpha]_D = -8.9^\circ$ (c = 1, CH₃OH)) which was converted to the corresponding diol base ($[\alpha]_D = +61.1^\circ$ (c = 1, CH₃OH)) and finally ringclosure reaction yielded 10 gr of (-)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = -12.1^\circ$ (c = 1, CH₃OH).

The oxalic acid salt of the (-)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D = -12.08^\circ$ (c = 1, CH₃OH).

EXAMPLE 3

Preparation of citalopram by method c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methanesulfonyl chloride in 30 ml of dichloromethane were added dropwise during 9 hour. The reaction mixture was washed with 0.1 M NaOH solution twice, the organic phase separated, dried (MgSO_4) and the solvent evaporated, leaving 21.5 gr of the title (\pm)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184-186°C.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in development of 5-HT syndrome (Christensen, Fjalland, Pedersen, Danneskiold-Samsøe and Svendsen; European J. Pharmacol. 41, 153-162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and a 5-HTP is used as a reference for full 5-HT syndrome

The route of administration

30 minutes after the administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5-10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: 1) excitation, 2) tremor, and 3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, ..., 9/9, where 0, 1, ..., 9 are the number of points per group after the dose in question. The ED_{50} value is calculated by log-probit analysis.

INHIBITION OF ^3H -SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of ^3H -serotonin (^3H -5-HT) (10 nM) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13-18; Hyttel, Prog.Neuro-Psychopharmacol. & Biol.Psychiat. 1982, 6, 277-295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146-153.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed by decapitation and exsanguinated. Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogenizer) in 40 vol (w/v) of icecold 0.32 M of sucrose containing 1 mM of nialamide. The P_2 fraction (synaptosomal fraction) is obtained by centrifugation (600 g, 10 min and 25000 g, 55 min, 4°C) and suspended in 800 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

To 4000 μl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 μl test substance in water. After preincubation at 37° for 5 min, 100 μl of ^3H -1-NA (final concentration 10 nM) are added and the samples are incubated for 10 min at 37°C. The incubation is terminated by filtering the samples under vacuum through Whatman GF/F filters with a wash of 5 ml buffer containing 10 μM of unlabelled 5-HT. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. Picofluor TM15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is

determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 μ M citalopram (Lu 10-171-B).

For determination of the inhibition of uptake five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC_{50} -value is determined as the concentration, at which the uptake is 50% of the total uptake in control samples minus the nonspecific binding and uptake in the presence of 10 μ M of citalopram.

Table 1

PHARMACOLOGICAL TEST RESULTS		
Compound	5-HTP pot. ED ₅₀ μ mol/kg	5-HT uptake inhibition IC ₅₀ (nM)
(+)-citalopram	2.0	1.1
(-)-citalopram	120	150
(\pm)-citalopram	3.3	1.8

(+)-1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ((+)-citalopram) and the non-toxic acid addition salts thereof may be administered to animals such as dogs, cats, horses, sheeps or the like, including human beings, both orally and parenterally, and may be used for example in the form of tablets, capsules, powders, syrups or in the form of the usual sterile solutions for injection. - Results upon administration to human beings have been very gratifying.

Most conveniently the compounds of Formula I are administered orally in unit dosage form such as tablets or capsules, each dosage unit containing the free amine or a non-toxic acid addition salt of one of the said components in an amount of from about 0.10 to about 100 mg, most preferably, however, from about 5 to 50 mg, calculated as the free amine, the total daily dosage usually ranging from about 1.0 to about 500 mg. The exact individual dosages as well as daily dosages in a particular case will, of course, be determined according to established medical principles under the direction of a physician.

When preparing tablets, the active ingredient is for the most part mixed with ordinary tablet adjuvants such as corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, or the like.

Typical examples of formulas for composition containing (+)-citalopram in the form of an acid addition salt as the active ingredient, are as follows:

1) Tablets containing 5 milligrams of (+)-citalopram calculated as the free base:	
Compound 20	5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:

(+)-citalopram	50 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

(+)-citalopram	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

(+)-citalopram	50 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:

(+)-citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, analgesics or antidepressants.

Also combinations of (+)-citalopram as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is a non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the

amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicylic, bismethylenesalicylic, propionic, gluconic, malic, malonic, mandelic, cannamic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may also be employed as acid addition saltforming acids.

When it is desired to isolate a compound of the invention in the form of the free base, this may be done according to conventional procedure as by dissolving the isolated or unisolated salt in water, treating with a suitable alkaline material, extracting the liberated free base with a suitable organic solvent drying the extract and evaporating to dryness or fractionally distilling to effect isolation of the free basic amine.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain physiological-psychological abnormalities of animals, especially depressions by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams/kg of body weight per day.

It is to be understood that the invention is not limited to the exact details of operation or exact compound or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

20 Claims

-1- (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

-2- The pamoic acid salt of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

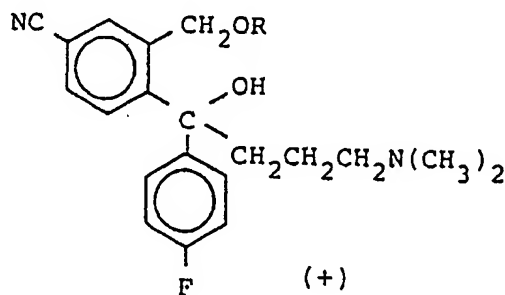
-3- A pharmaceutical composition in unit dosage form comprising as an active ingredient, a compound as defined in claim 1.

-4- A pharmaceutical composition in unit dosage form comprising, as an active ingredient, the compound of claim 2.

-5- A pharmaceutical composition in unit dosage form, according to claim 3 or 4, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

-6- A method for the preparation of a compound as defined in claim 1, which comprises, converting (+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile or a monoester thereof in a stereoselective way to (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

-7-



wherein R is hydrogen or F, a labile ester group.

-8- A method for the preparation of 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile in the form of a racemic mixture which comprises treating 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl) benzonitrile, esterified at the primary alcohol group with an acid, forming a labile ester, with an agent causing ringclosure and isolating the compound formed as the free base or a pharmaceutically acceptable acid addition salt thereof.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 89 30 5532

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	CHEMICAL ABSTRACTS, vol. 104, no. 19, 12th May 1986, page 43, abstract no. 161810v, Columbus, Ohio, US; M. HIBERT et al.: "Stereoselective blockade at the 5-HT autoreceptor and inhibition of radioligand binding to central 5-HT recognition sites by the optical isomers of methiothepin", & NEUROPHARMACOLOGY 1986, 25(1), 1-4 ---	1-8	C 07 D 307/87 A 61 K 31/34 // C 07 B 57/00 C 07 C 121/80 C 07 C 143/68
D,A	EP-A-0 171 943 (H. LUNDBECK) * Whole document * ---	1-8	
D,A	US-A-4 136 193 (K.P. BOGESO) * Whole document * -----	1-8	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 307/00 C 07 C 121/00 C 07 C 143/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 30-08-1989	Examiner ALLARD M.S.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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- (72) Inventors; and
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(54) Title: TREATMENT OF NEUROTIC DISORDERS

(57) Abstract: Use of the escitalopram (the S-(+)-enantiomer of citalopram) or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders is provided, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

TREATMENT OF NEUROTIC DISORDERS

Field of invention

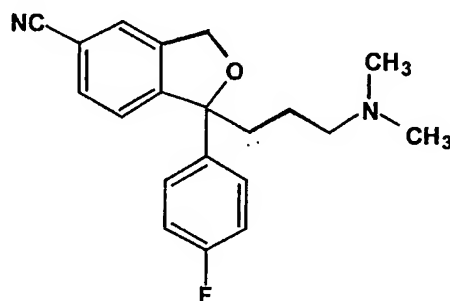
- 5 The present invention relates to the use of the compound escitalopram (INN-name), which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethyl-amino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, or a pharmaceutically acceptable salt thereof for the preparation of medicaments for the treatment of neurotic disorders, including anxiety states and panic attacks.

10

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:

15



Formula I

- It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 1982, 6, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, 1987, 75, 478-486, and it is now marketed for the treatment of depression and panic disorders. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

25

Escitalopram and a method for its preparation are disclosed in US Patent No 4,943,590. The stereo selectivity of citalopram, i.e. the 5-HT-reuptake inhibition in the S-enantiomer, and accordingly, the antidepressant effect of said enantiomer is also disclosed. S-citalopram is now in development as an antidepressant.

30

Studies have shown that patients suffering from neurotic disorders including anxiety disorders, especially generalised anxiety, and panic attacks, in particular in association with agoraphobia, have a quality of life impairment comparable with or greater than the disability found in patients with alcoholism, schizophrenia or personality disorders. Furthermore, current treatments are not always effective or cause unacceptable side effects.

Consequently, there is a need for alternative therapies useful in the treatment of neurotic disorders.

Escitalopram has now been found to show potent effects in models of neurotic disorders such as anxiolytic effect and prominent effect in the treatment of panic attacks and obsessive compulsive disorder.

Description of the Invention

According to the present invention, a novel use of escitalopram, namely for the preparation of a medicament useful in the treatment of neurotic disorders is provided.

Throughout this specification and claims the term neurotic disorders is used to designate a group of mental disorders, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

The terms generalised anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder are as defined in DSM IV.

The phrase "panic attacks" contemplates treatment of any disease, which is associated with panic attacks including panic disorder, specific phobias, social phobia and agoraphobia in which panic attacks occur. These disorders are further defined in the DSM IV. A panic attack is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror, often associated with feelings of impending doom. During the attack, symptoms such as palpitations, sweating, trembling, sensations of shortness of breath,

feeling of choking, chest pain or discomfort, nausea, feeling dizzy, feelings of unreality, fear of losing control or going crazy, fear of dying, paresthesias and chills or hot flushes are present.

- 5 Panic disorders are characterised by recurrent unexpected panic attacks about which there is a persistent concern. Agoraphobia is anxiety about, or avoidance of, places or situations from which escape might be difficult or in which help may not be available in the event of a panic attack. Specific phobia and social phobia (together formerly simple phobia) are characterised by marked and persistent fear that is excessive or unreasonable, cued by the
10 presence or anticipation of a specific object or situation (flying, heights, animals, seeing blood etc.) or social performance situations.

The disorders in which panic attacks occur are differentiated from each other by the predictability of the occurrence of the attacks, for example, in panic disorder the attacks are
15 unpredictable and not associated with any particular event, whereas in specific phobia the attacks are triggered by specific stimuli.

The phrase "treatment of panic disorder" means a reduction in the number or prevention of attacks and/or relief of the severity of the attacks. Similarly, the treatment of generalised
20 anxiety disorder, social anxiety disorder, post traumatic stress disorder and obsessive compulsive disorder include the treatment or prevention of these diseases, or the relief of the symptoms thereof.

According to the invention, escitalopram may be used as the base of the compound or as a
25 pharmaceutically acceptable acid addition salt thereof or as an anhydrate or hydrate of such salt. The salts of the compound used in the invention are salts formed with non-toxic organic or inorganic acids, in particular the oxalate.

Escitalopram has been found to show prominent effects different from the effects of the
30 racemate in the "Inhibition of footshock-induced ultrasonic vocalisation in adult rats" - test, the "Mice Black and White Test" setup, and in the polydipsia test. These models are standard

animal models for anxiolytic effect and effect on panic attacks and for obsessive compulsive disorder, respectively.

According to the invention, escitalopram or a pharmaceutically acceptable salt thereof may
5 be administered in any suitable way e.g. orally or parenterally, and it may be presented in
any suitable form for such administration, e.g. in the form of tablets, capsules, powders,
syrups or solutions or dispersions for injection. Preferably, and in accordance with the
purpose of the present invention, the compound of the invention is administered in the form
of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a
10 suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art.
Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants
and/or diluents and subsequently compressing the mixture in a convenient tableting
15 machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum,
magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive
such as colourings, flavourings, preservatives, etc. may also be used provided that they are
compatible with the active ingredients.

20 The compound of the invention is most conveniently administered orally in unit dosage
forms such as tablets or capsules, containing the active ingredient in a dose from about 1.0
mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.

The oxalate of escitalopram may be prepared as described in US Patent No 4,943,590 and
25 the base and other pharmaceutically acceptable salts may be obtained therefrom by standard
procedures.

Thus the acid addition salts used according to the invention may be obtained by treatment of
escitalopram with the acid in an inert solvent followed by precipitation, isolation and
30 optionally re-crystallisation by known methods and if desired micronisation of the crystalline
product by wet or dry milling or another convenient process, or preparation of particles from
a solvent-emulsification process.

Pharmacological Tests

Escitalopram was tested in well recognised and reliable test models of effects on neurotic disorders. Citalopram-racemate was included for comparison purposes.

5

The footshock- induced vocalisation test in adult rats.

The footshock- induced vocalisation test in adult rats (described in detail in Sánchez C., Effect of serotonergic drugs on footshock-induced ultrasonic vocalization in adult male rats. *Behav. Pharmacol.* 1993; 4:267-277) is a test for anxiolytic and anti-panic effects.

10

Experimental Procedure

Male rats (Wistar WU, Charles River, Germany), weighing 150-175 g at the beginning of the study were used.

Briefly, test cages (22 cm x 22 cm x 22 cm) made of grey Perspex and equipped with a metal
15 grid floor were used. Footshocks were delivered from a two pole shocker and a microphone sensitive to ultrasounds in the range of 20-30 kHz was placed in the centre of the lid of the test cage. The ultrasounds were sent from the microphone to a preamplifier and converted from AC signals to DC signals in a signal rectifier. The accumulated time, in which the voltage of the rectified signal was larger than the voltage of a previously determined threshold
20 level, was recorded.

Twenty-four hours before the first test session the animals were primed. A rat was placed in each test cage and received, immediately thereafter, four 1.0 mA inescapable footshocks each of a duration of 10 sec and with an intershock interval of 5 sec. The animals were left
25 in the test cage for 6 min after the last shock. On test days, drug or saline was given 30 min before test. The rats received four 1.0 mA inescapable footshocks each of a duration of 10 sec. The intershock interval was 5 sec. Recording of ultrasonic vocalisation started 1 min after the last shock and lasted for 5 min. The total time spent on vocalisation was recorded. After a wash-out period of one week the rats were used in a new test session. The rats were
30 used for a total of 7-8 weeks. At each test session, the animal groups were randomly allocated to treatment with saline or test drug. Each treatment group consisted of 8 animals,

one saline and 2-4 drug treated groups were included at each session. Each drug was tested at least in two separate experiments with overlapping doses.

Results

- 5 The experiments showed that the maximum effect was 60-70% inhibition for citalopram-racemate whereas escitalopram was able to inhibit vocalisation completely.

Black and White Box Test

- This is a test for anxiolytic effects. The test model is further described in Sánchez, C. (1995)
10 Pharmacol. Toxicol. 77, 71-78.

Test procedure

- Male mice (Lundbeck strain, Charles River, Germany) weighing 30-35 g were housed in groups of 4 in macrolon cages type II under a reversed 12 h day /night cycle (lights off 7
15 p.m.). The mice were adapted to the reversed light/dark cycle for at least 3 weeks prior to testing. The room temperature ($21 \pm 2^\circ\text{C}$), relative humidity ($55 \pm 5\%$), and air exchange (16 times per h) were automatically controlled. The animals had free access to commercial food pellets and water.

- The test box used was designed as described by Sánchez (1995) (*supra*). Briefly, the test box
20 (45 cm x 27 cm x 27 cm) was open-topped and divided into two compartments (ratio 2:3) by a partition which was black on the side facing the black compartment and white on the side facing the white compartment. The smaller chamber was made of black perspex. The larger chamber was made of white perspex except for the lowest 7.5 cm. This part was made of transparent perspex (outer walls) and black perspex (partition). The white compartment was
25 connected to the black compartment by a 7.5 cm x 7.5 cm opening in the partition. The floor of the white compartment was divided into 9 fields, and the floor of the black was divided into 6 fields. The white compartment was illuminated by means of a Schott KL 1500 electronic lamp emitting cold light corresponding to a light intensity of 560 Lux. The mouse test-system was fully automated by 2 rows of 11 infrared light sources and photocells in the
30 transverse direction and 1 row of 16 in the longitudinal direction (lower row). The lower row of photocells (2 cm above cage floor) detected horizontal locomotor activity (crossing, entries, and time in each compartment), whereas the upper row of photocells (5 cm above

cage floor) detected rearing activity. The accumulated data for 1 min intervals were recorded from 4 test boxes simultaneously and stored in a Paradox data base.

The test boxes were placed in a dark and quiet room. The mice were transported to the test room in a darkened container about 2 h before test. The test room was separated into two parts by a black curtain. The drug treatment took place in one part of the room using a minimum of red light. After dosing, the mice were placed individually in macrolon type II cages until test. The pretreatment time was 30 min. The test boxes were placed in the other part of the room. The test was started by placing the mouse in the centre of the brightly-lit white compartment facing the opening to the black compartment. The test duration was 5 min and the number of rears and line crossings between squares in both the black and the white compartment, number of entries into the black compartment and time spent in the white compartment were assessed.

Results

Escitalopram showed prominent effects in this model.

Schedule-induced Polydipsia

Food deprived rats exposed to a procedure in which food is delivered intermittently will drink large amounts of water if given the opportunity to do so. This behavioural phenomenon is called schedule-induced polydipsia and can be considered as an excessive expression of a normal behaviour. Schedule-induced polydipsia is regarded as a model of obsessive-compulsive disorder (Woods et al. 1993).

Test Procedure:

Male wistar rats (Møllegaard) housed in pairs and kept on a food-restricted diet (80% of normal body weight) for 2 weeks before the start of testing and throughout the duration of testing. To induce polydipsia rats were placed in test chambers where a pellet dispenser automatically dispensed one 60 mg food pellet every 60 seconds. Water was available at all times in the test chamber. Rats were tested 4-5 times per week, after 3-4 weeks training 70% of the rats were drinking >10ml per 30 min test session.

Once the rats had attained a steady drinking level compounds could be tested. Citalopram (40 mg/kg) or Lu 26-054 (20 mg/kg) were administered orally 60 min prior to testing and at

10:00 on the non-test days. The water intake was presented as a percentage of the pre-dosing (baseline) level.

Results:

- 5 Escitalopram produced a significant reduction in water intake, whereas citalopram was without effect.

All these studies show that escitalopram has potent anti neurotic diseases effects, in particular anxiolytic effects and effects on panic attacks and obsessive compulsive disorder.

Claims

1. Use of escitalopram or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders.
- 5 2. The use according to Claim 1, **characterised in**, that the medicament is for administration as a unit dose.
3. The use according to Claim 1 or 2, **characterised in**, that the unit dose is containing the
10 active ingredient in an amount from 1.0 mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.
4. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of generalised anxiety disorder.
- 15 5. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of social anxiety disorder.
6. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment
20 of post traumatic stress disorder.
7. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of obsessive compulsive disorder.
- 25 8. Use of any of Claims 1 to 3, **characterised in**, that the medicament is for the treatment of panic attacks.
9. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of panic disorder.

10. Use of any of Claim 8, characterised in, that the medicament is for the treatment of specific phobias.
11. Use of any of Claim 8, characterised in, that the medicament is for the treatment of
5 social phobia.
12. Use of any of Claim 8, characterised in, that the medicament is for the treatment of agoraphobia.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00377

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/343, A61P 25/00, A61P 25/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, MEDLINE, CAPLUS, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Rev. Contemp. Pharmacother, Volume 10, 1999, A. F. Joubert et al., "Citalopram and Anxiety Disorders" page 79 - page 131 --	1-12
X	ACTA PSYCHIATRICA SCANDINAVICA, Volume 96, 1997, Koponen H. et al., "Citalopram an the treatment of obsessive-compulsive disorder: an open pilot study" page 343 - page 346 --	1-3,7
X	Journal of Serotonin Research, Volume 1, 1996, Dan J. Stein MB et al., "Use of serotonin selective reuptake inhibitor citalopram in obsessive-compulsive disorder" page 29 - page 33 --	1-3,7

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00377

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J Clin Psychiatry, Volume 59, No 10, October 1998, Ulla M. Lepola et al., "A Controlled, Prospective, 1-Year Trial of Citalopram in the Treatment of Panic Disorder" page 528 - page 534 --	1-3,8-12
P,X	WO 0015220 A1 (ASTRA AKTIEBOLAG), 23 March 2000 (23.03.00) --	1-12
A	US 4943590 A (KLAUS P. BOEGESOE ET AL), 24 July 1990 (24.07.90), column 2, line 38 - line 40 --	1-12
A	US 5296507 A (TANAKA, Y. ET AL.), 22 March 1994 (22.03.94) --	1-12
P,A	WO 0034263 A1 (H. LUNDBECK ET AL), 15 June 2000 (15.06.00) -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

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International application No.

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